# Antithrombotic Strategy in HBR Patients: Updated Strategy

**Joo-Yong Hahn, MD/PhD**
Heart Vascular Stroke Institute,
Samsung Medical Center, Seoul, Korea

# Disclosure

- Grant support
  - Korean Society of Interventional Cardiology
  - Ministry of Health & Welfare, Republic of Korea
  - Sungkyunkwan University Foundation for Corporate Collaboration
  - Abbott Vascular, Boston Scientific, Biotronik, Daiichi Sankyo, and Medtronic

- Consulting Fees/Honoraria
  - Abbott Vascular, Astra Zeneca, Biotronik, Biometrics, Daiichi Sankyo, Pfizer, and Sanofi-Aventis

# Strategies to reduce the risk of bleeding after PCI




Ref. Presented by Angiolilio at TCTAP 2019

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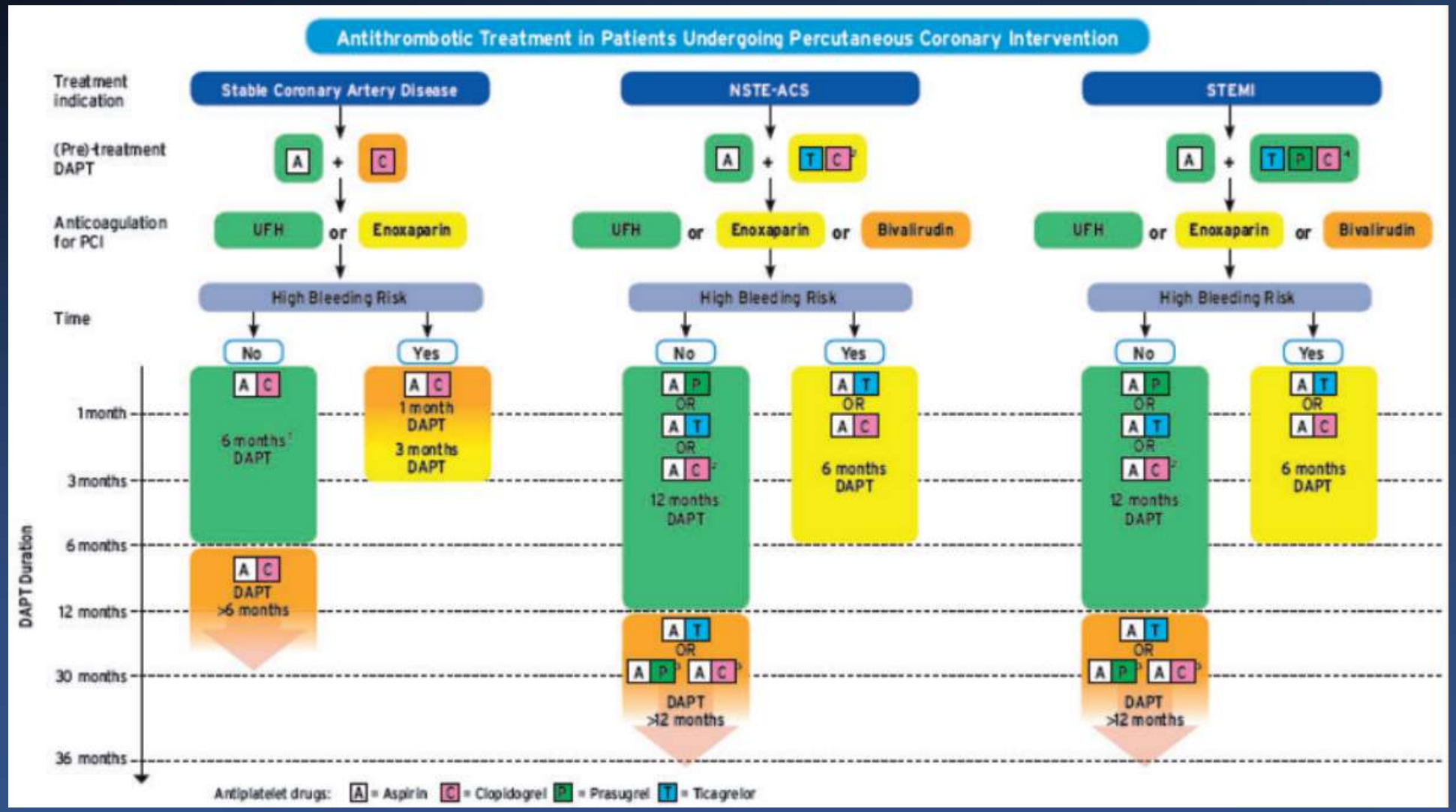
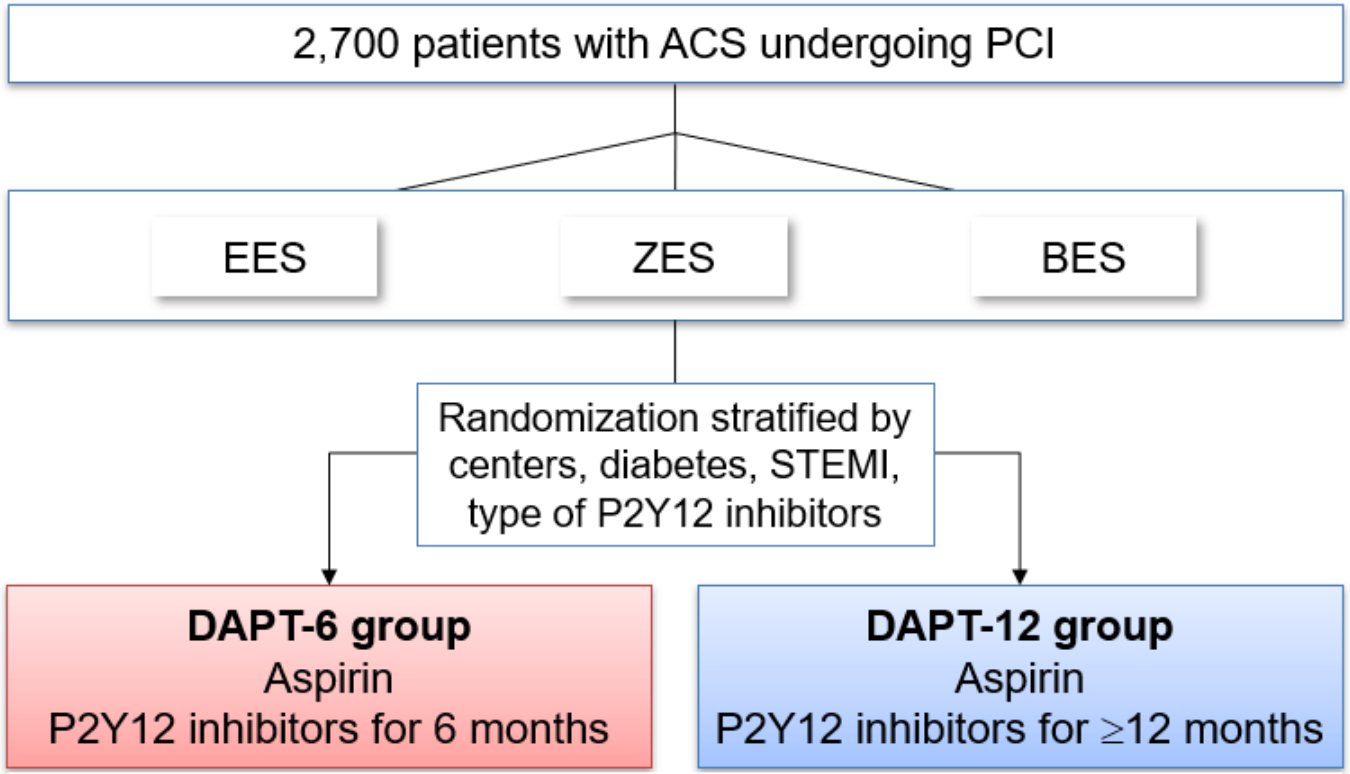
# 2018 ESC/EACTS Guidelines on myocardial revascularization



# SMART-DATE trial: study design

A prospective, multicenter, randomized, and open-label trial




Primary endpoint: 18-month MACCE
a composite of all-cause mortality, MI, or cerebrovascular events

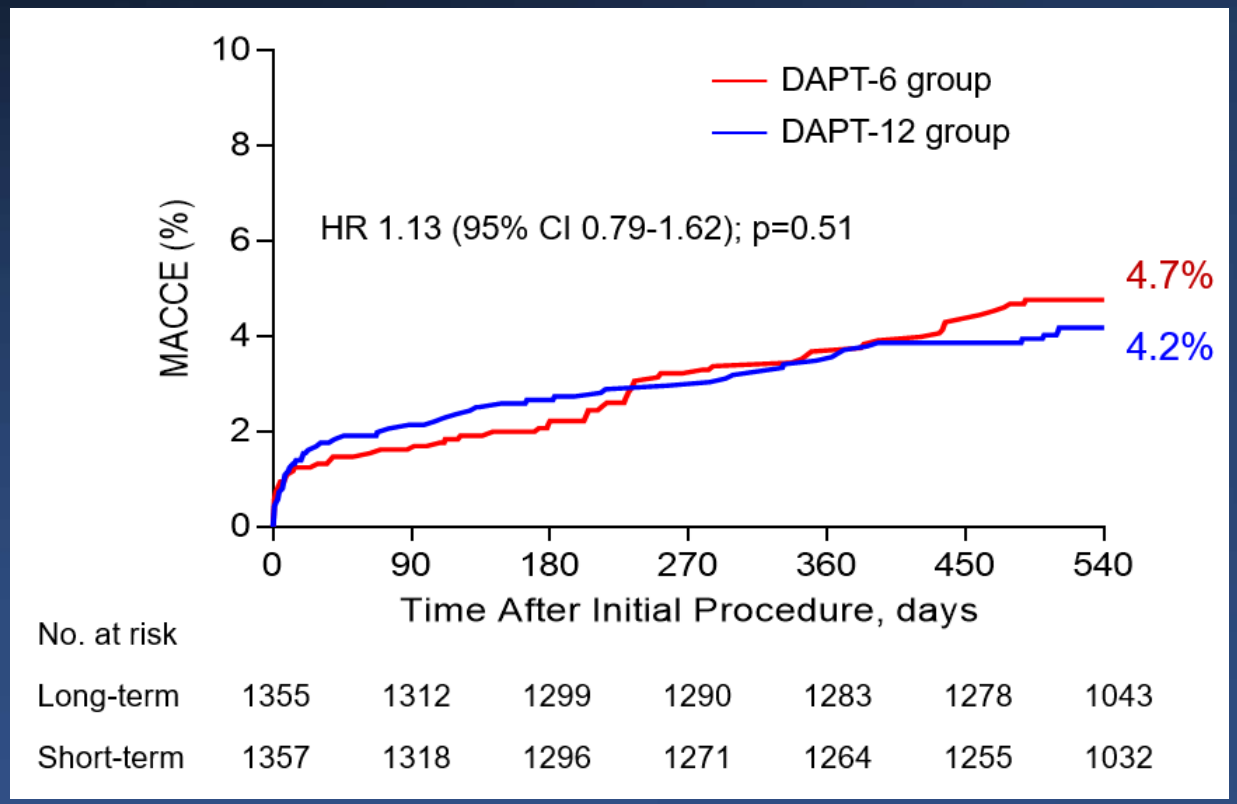
ClinicalTrials.gov NCT01701453

- PCI=percutaneous coronary intervention
- EES = everolimus eluting stent (Xience Prime)
- ZES = zotarolimus eluting stent (Resolute Integrity)
- BES = biolimus eluting stent (Biomatrix Flex)
- STEMI = ST elevation myocardial infarction
- MI = myocardial infarction

Lee JM, Hahn JY, …, Gwon HC. Am Heart J 2016

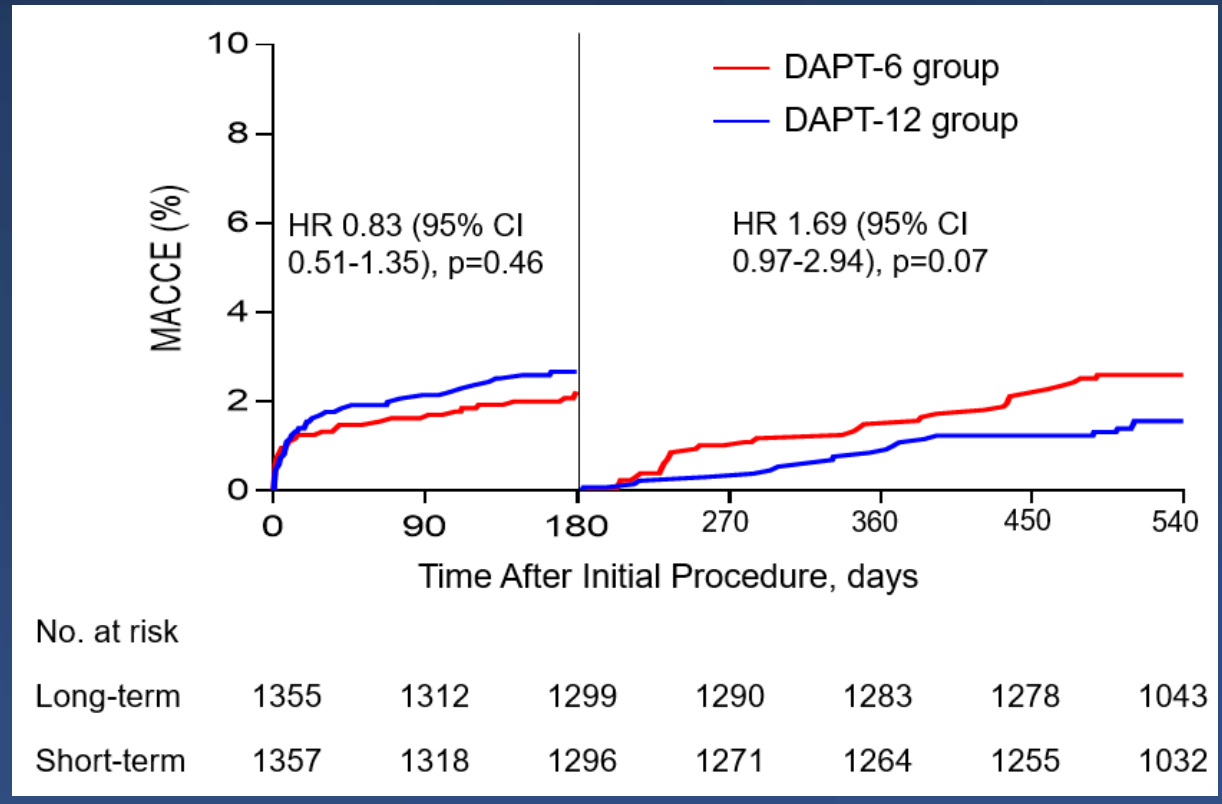
# Primary end point (MACCE)

**Difference, 0.5%; upper limit of 1-sided 95% CI, 1.8%; P=0.03 for noninferiority with a predefined non-inferiority margin of 2.0%**




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Long-term | 1355 | 1312 | 1299 | 1290 | 1283 | 1278 | 1043 |
| Short-term | 1357 | 1318 | 1296 | 1271 | 1264 | 1255 | 1032 |

**Landmark analysis at 6 months**

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|---|---|---|---|---|---|---|---|
| Long-term | 1355 | 1312 | 1299 | 1290 | 1283 | 1278 | 1043 |
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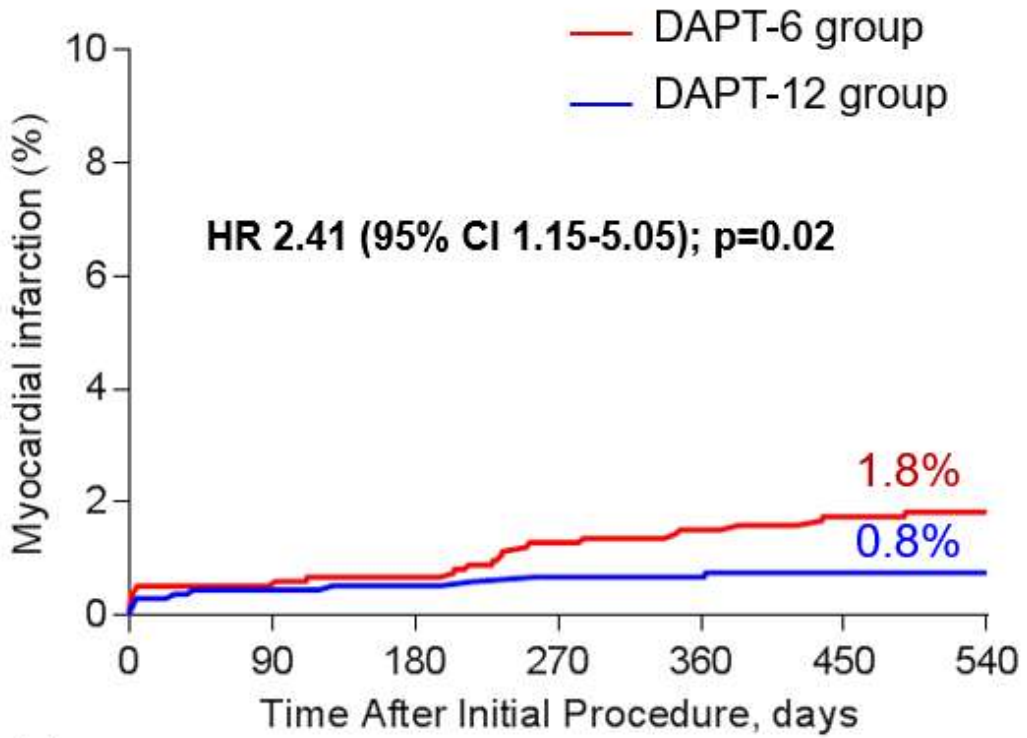
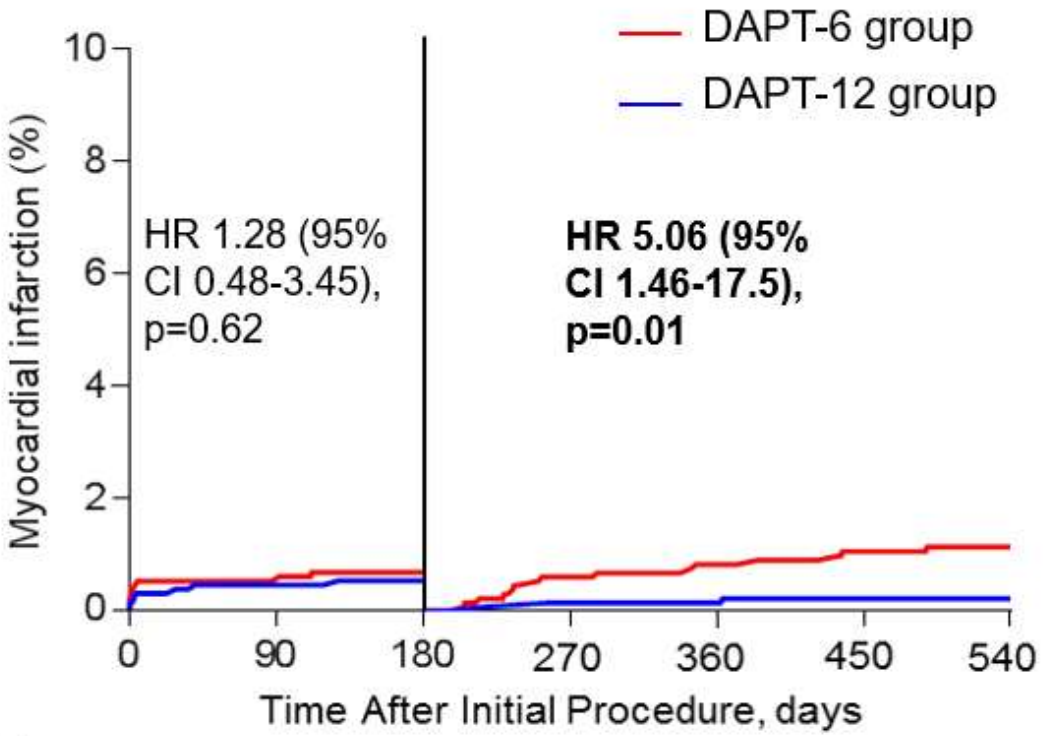
Hahn JY, Song YB,…, Gwon HC. Lancet 2018

# Myocardial infarction




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Long-term | 1355 | 1315 | 1303 | 1295 | 1289 | 1284 | 1049 |
| Short-term | 1357 | 1321 | 1300 | 1277 | 1270 | 1263 | 1039 |




No. at risk

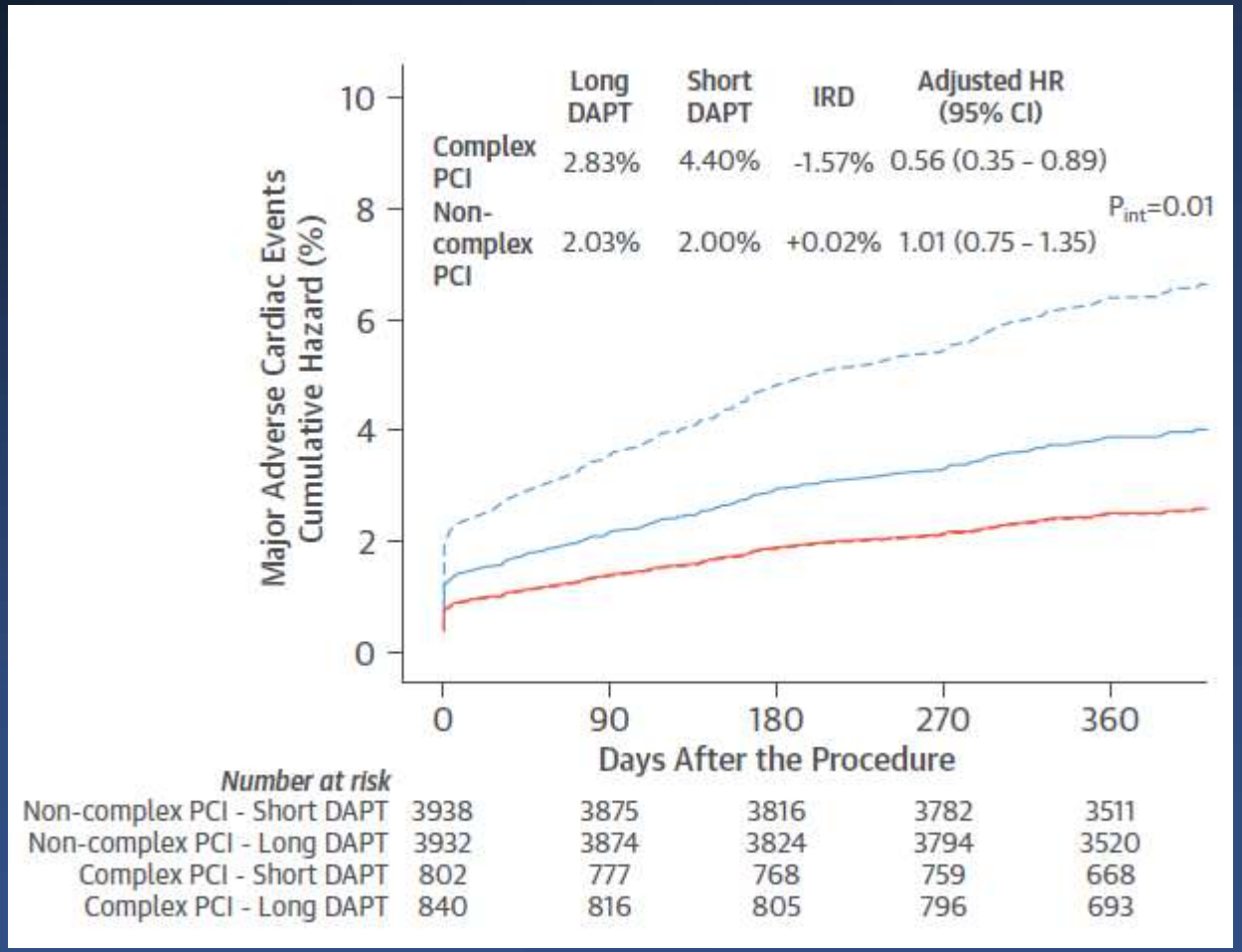
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Long-term | 1355 | 1315 | 1303 | 1295 | 1289 | 1284 | 1049 |
| Short-term | 1357 | 1321 | 1300 | 1277 | 1270 | 1263 | 1039 |

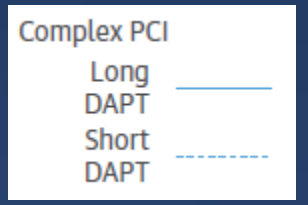


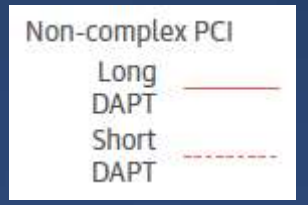
Hahn JY, Song YB,…, Gwon HC. Lancet 2018

# Long- Versus Short-Term DAPT in Patients With or Without Complex PCI

## Cardiac death, MI, or ST




J Am Coll Cardiol 2016;68:1851–64

# Strategies to reduce the risk of bleeding after PCI

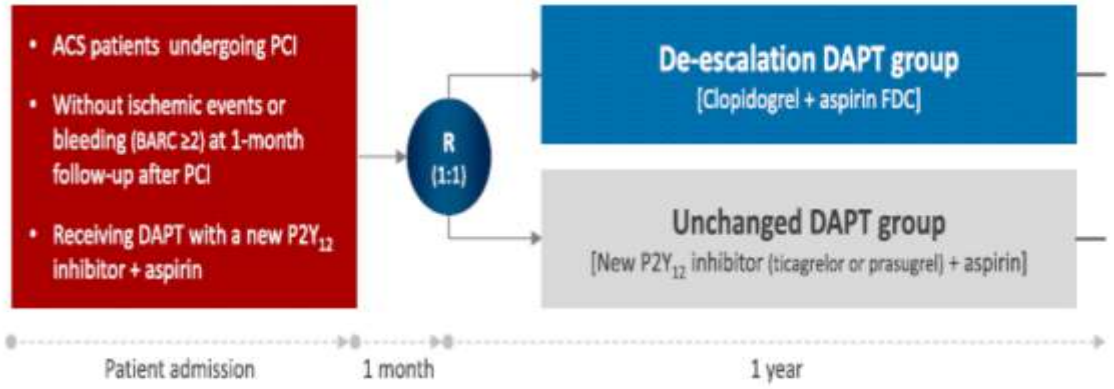
**Not for all**
**: ACS, complex PCI**


**SMART-DATE**


# De-escalation strategy: switching to clopidogrel

## TOPIC[1]

- **Objective:** To investigate the impact of switching from aspirin plus a newer $P2Y_{12}$ blocker to a fixed dose combination (FDC) of aspirin and clopidogrel, in patients with no adverse event during the first month after ACS.
- **An open-label, prospective, single centre, randomized, controlled trial in 646 ACS patients**



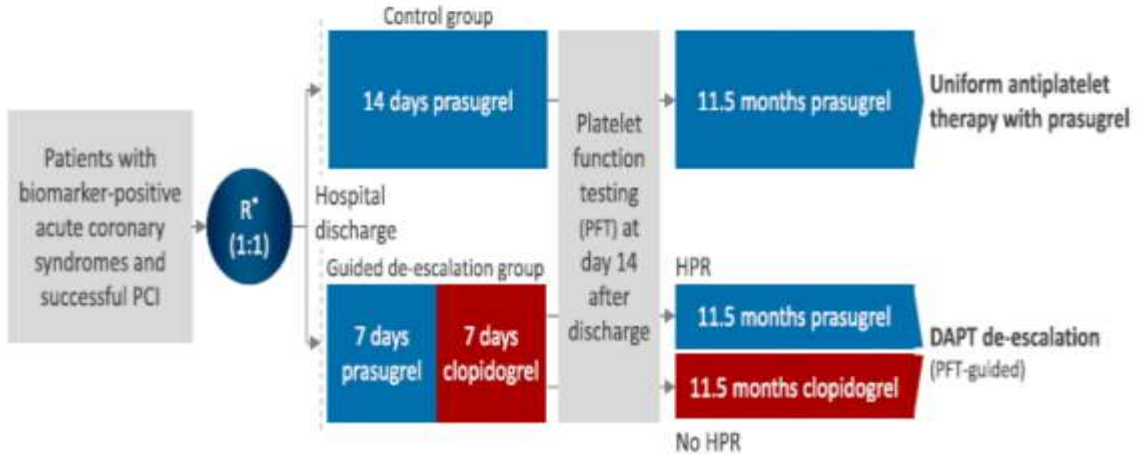

**Composite primary endpoint**
- CV death, urgent revasc., stroke, and BARC ≥2

**Secondary endpoints**
- Components of primary endpoint - Death, MI, stroke, BARC bleeding ≥2

## TROPICAL-ACS[2]

- **Objective:** To investigate the safety and efficacy of early de-escalation of antiplatelet treatment from prasugrel to clopidogrel guided by platelet function testing (PFT) in patients with acute coronary syndrome undergoing PCI.

| Design | Interventions | Primary endpoint |
|---|---|---|
| Prospective, randomized open-label study in 2,619 ACS patients | • Prasugrel 5 or 10 mg<br>• Day 0–7 prasugrel 5 or 10 mg, day 8–14 clopidogrel 75 mg<br>- If HPR on Day 14, return to prasugrel<br>- No HPR on Day 14, remain on clopidogrel for 11.5 months | CV death, MI, stroke and BARC bleeding grade ≥2 at 12 months |

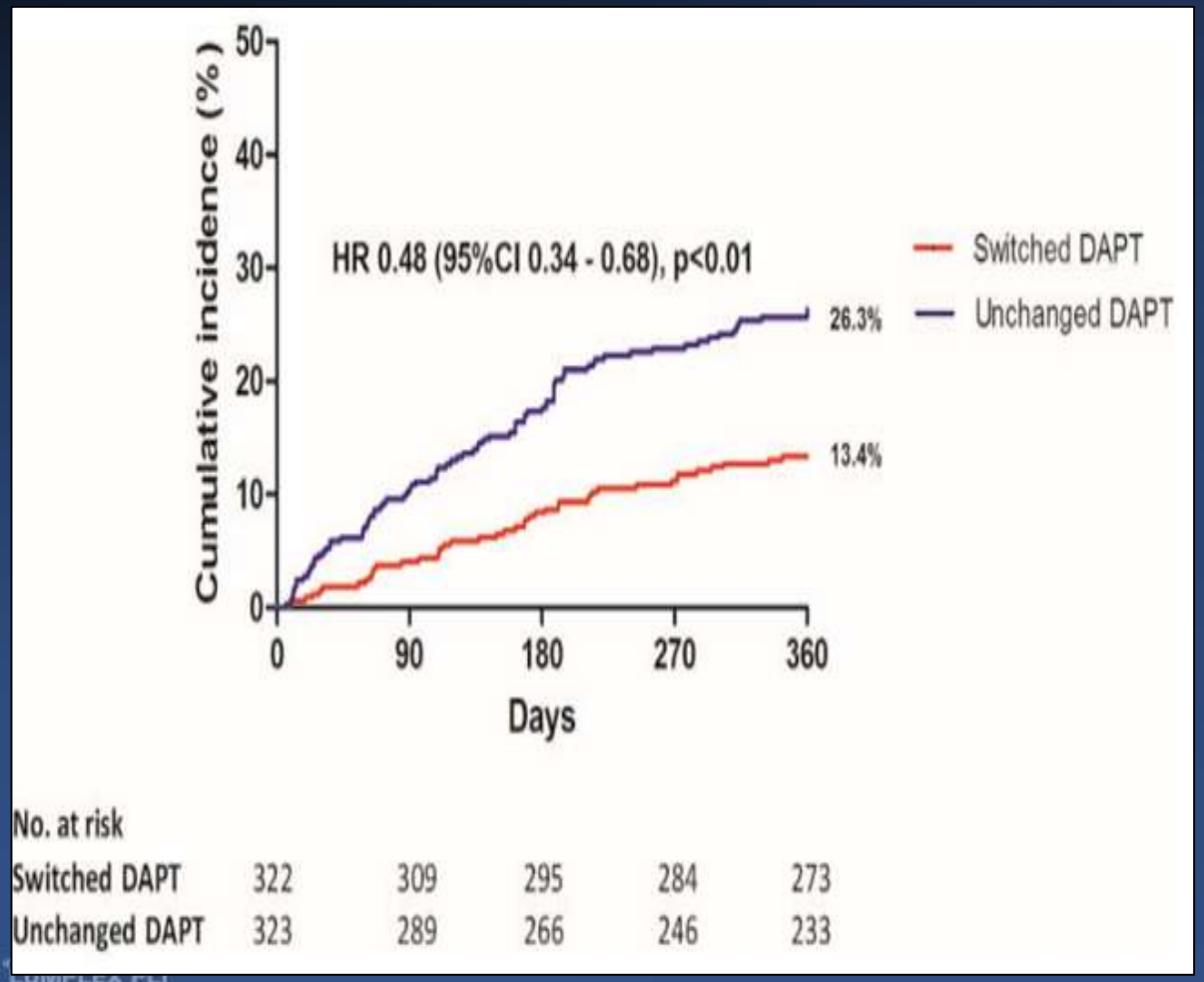




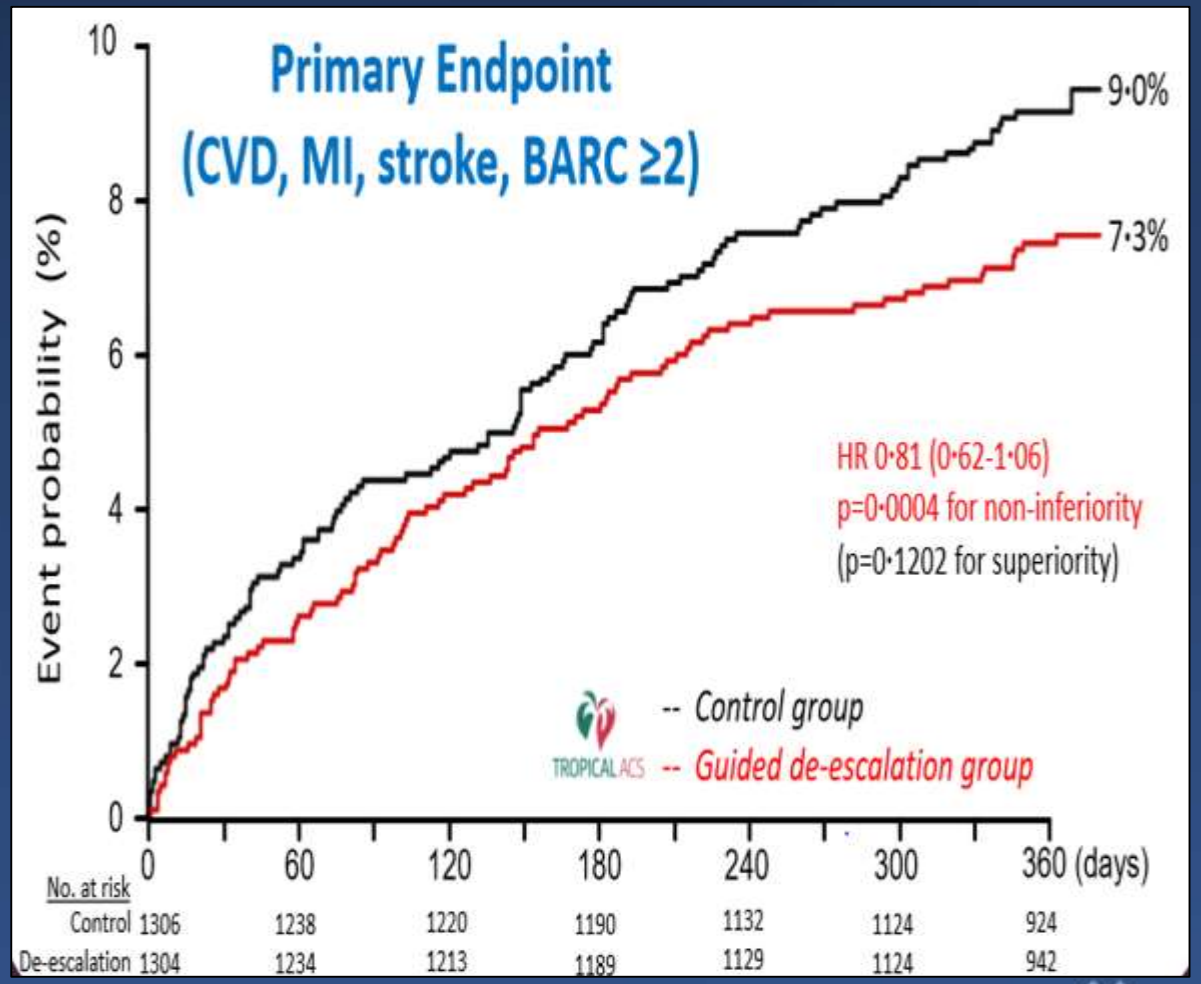

Ref. 1. Cuisset T et al. Eur Heart J 2017;38:3070–8; 2. Sibbing D et al. Lancet 2017;390:1747–57.

# De-escalation strategy: Non-inferior to continuous DAPT with potent P2Y12 inhibitors

## TOPIC[1]




## TROPICAL-ACS[2]




Ref. 1. Cuisset T et al. Eur Heart J 2017;38:3070–8; 2. Sibbing D et al. Lancet 2017;390:1747–57.

# Limitations of De-escalation studies

- Open-label study design
- Modest population size
- Combined safety and efficacy endpoint
- Bleeding endpoint includes minor bleeding events

# Strategies to reduce the risk of bleeding after PCI

**Not for all**
**: ACS, complex PCI**


**SMART-DATE**

**Limited data**


**TOPIC**
**TROPICAL-ACS**
**TALOS**

# Trials on P2Y12 inhibitor monotherapy

| Name | Population | Randomization | Allocation | P2Y12 inhibitor | Primary endpoint | Primary endpoint analysis | Key exclusion criteria | Sample size |
|---|---|---|---|---|---|---|---|---|
| **SMART-CHOICE** | ACS and stable CAD | Within 3 months after procedure | P2Y12 inhibitor monotherapy vs. DAPT | Clopidogrel, Prasugrel, or Ticagrelor | All-cause mortality, MI, or Stroke | 12M after index procedure | DES implantation within the last 12 months prior to randomization | 3000 |
| **GLOBAL LEADERS** | ACS and stable CAD | Before index procedure | Ticagrelor monotherapy vs. DAPT | Ticagrelor | All-cause mortality or non-fatal MI | 24M after index procedure | Need for anticoagulation | 16000 |
| **TWILIGHT** | ACS and stable CAD with high risk feature | 3 months after procedure | Ticagrelor monotherapy vs. DAPT | Ticagrelor | Bleeding | 15M after index procedure | STEMI, Need for anticoagulation | 9000 |
| **TICO** | ACS | 3 months after procedure | Ticagrelor monotherapy vs. DAPT | Ticagrelor | MACCE + TIMI major bleeding | 12M after index procedure | Need for anticoagulation | 3056 |
| **STOPDAPT-2** | ACS and stable CAD | At the index procedure | Clopidogrel vs. DAPT then Clopidogrel vs. ASA | Clopidogrel | CV death/MI/definite ST/stroke/bleeding | 12M after index procedure | Need for anticoagulation | 3045 |

# SMART-CHOICE trial

Comparison between P2Y12 Antagonist MonotHerapy and Dual Antiplatelet Therapy in Patients UndergOing Implantation of Coronary Drug-Eluting Stents

A prospective, multicenter, randomized, open-label, noninferiority trial

Key exclusion criteria
- Active bleeding
- DES implantation within 12 months
- Contraindication to study medication

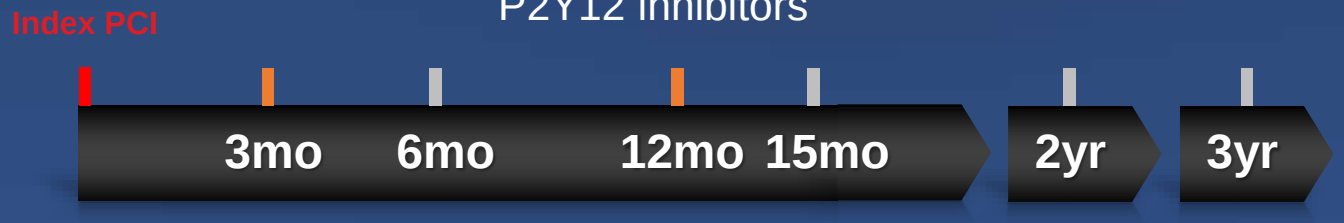
**3000 Patients Matching Enrollment Criteria**

**Percutaneous Coronary Intervention (CoCr-EES, PtCr-EES, and SES with bioresorbable polymer) + 3-month DAPT**

**P2Y12 inhibitors alone**
**N=1500**

Stratified by
Center
Stent
ACS
P2Y12 inhibitors

**Aspirin + P2Y12 inhibitors**
**N=1500**

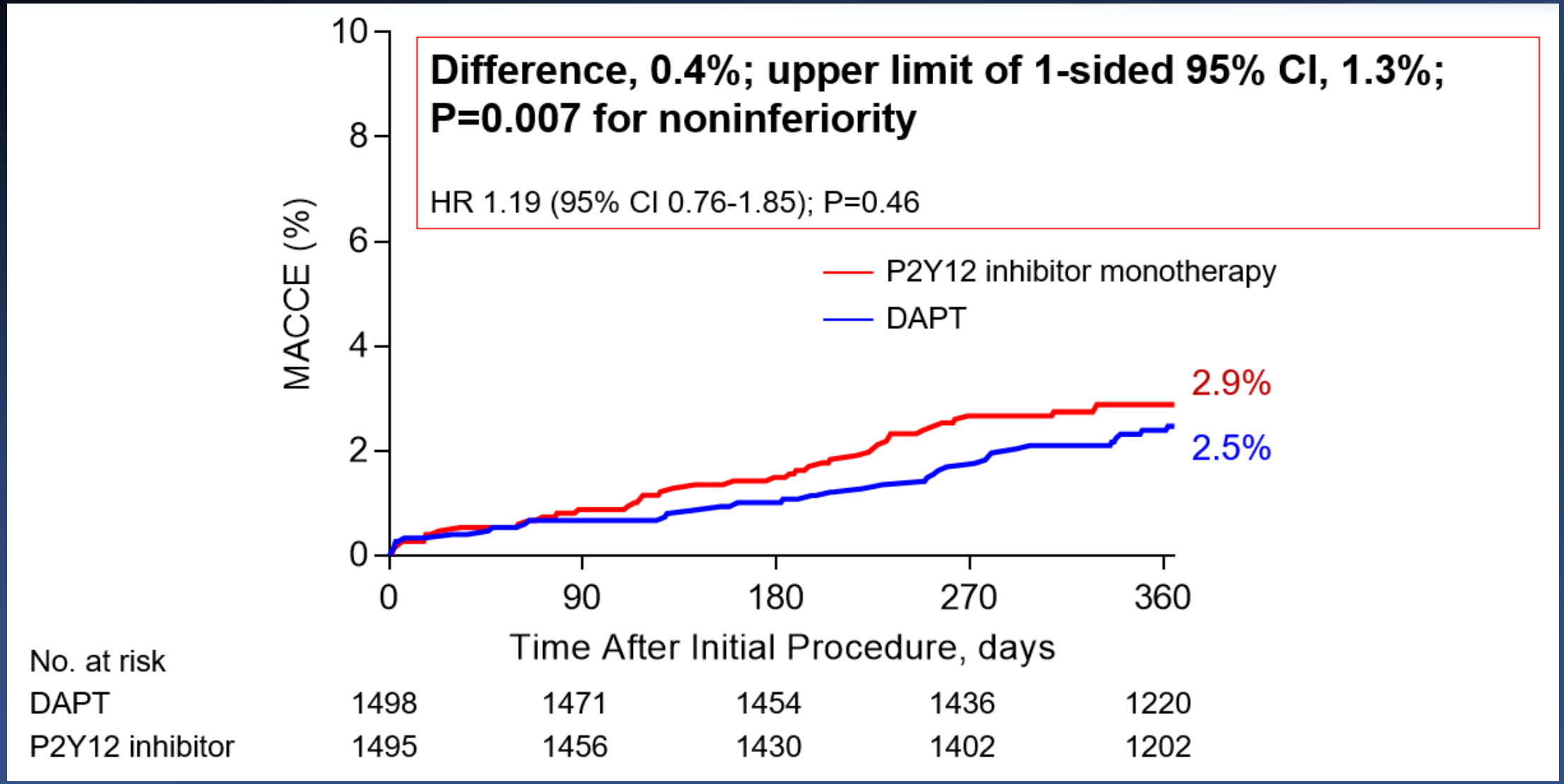



**1° EP: death, MI, or stroke**

ClinicalTrials.gov Identifier: NCT02079194

Song YB, Hahn JY,…, Gwon HC. Am Heart J 2018.

# Primary end point (MACCE)






Hahn JY, Song YB,…, Gwon HC. JAMA 2019.

# Clinical outcomes at 12 months

| Outcome | P2Y12 inhibitor monotherapy (n=1495) | Dual antiplatelet therapy (n=1498) | HR (95% CI) | P Value |
|---|---|---|---|---|
| MACCE | 42 (2.9%) | 36 (2.5%) | 1.19 (0.76-1.85) | 0.46 |
| Death | 21 (1.4%) | 18 (1.2%) | 1.18 (0.63-2.21) | 0.61 |
| Myocardial infarction | 11 (0.8%) | 17 (1.2%) | 0.66 (0.31-1.40) | 0.28 |
| Stroke | 11 (0.8%) | 5 (0.3%) | 2.23 (0.78-6.43) | 0.14 |
| Death or myocardial infarction | 31 (2.1%) | 32 (2.2%) | 0.98 (0.60-1.61) | 0.94 |
| Cardiac death | 11 (0.8%) | 13 (0.9%) | 0.86 (0.38-1.91) | 0.70 |
| Cardiac death or myocardial infarction | 22 (1.5%) | 27 (1.9%) | 0.83 (0.47-1.45) | 0.50 |
| Stent thrombosis | 3 (0.2%) | 2 (0.1%) | 1.51 (0.25-9.02) | 0.65 |
| Bleeding BARC type 2-5 | 28 (2.0%) | 49 (3.4%) | 0.58 (0.36-0.92) | 0.02 |
| Major bleeding | 12 (0.8%) | 14 (1.0%) | 0.87 (0.40-1.88) | 0.72 |
| Net adverse clinical and cerebral events | 65 (4.5%) | 81 (5.6%) | 0.81 (0.58-1.12) | 0.20 |

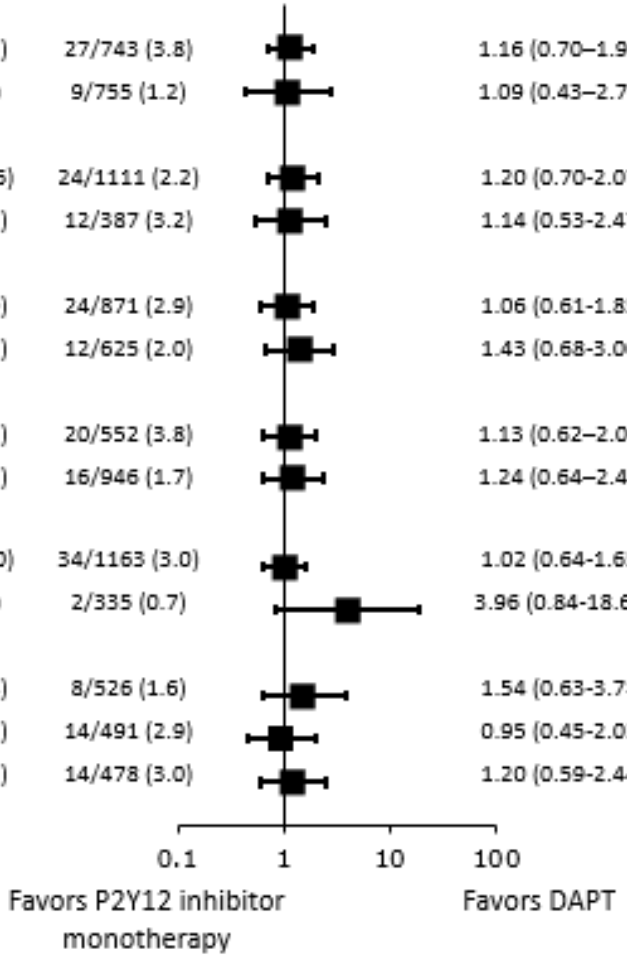
Major bleeding was defined as BARC type 3-5 bleeding.
Net adverse clinical and cerebral events were defined as MACCE plus BARC type 2-5 bleeding.



Hahn JY, Song YB,…, Gwon HC. JAMA 2019.

# Subgroup analysis: MACCE

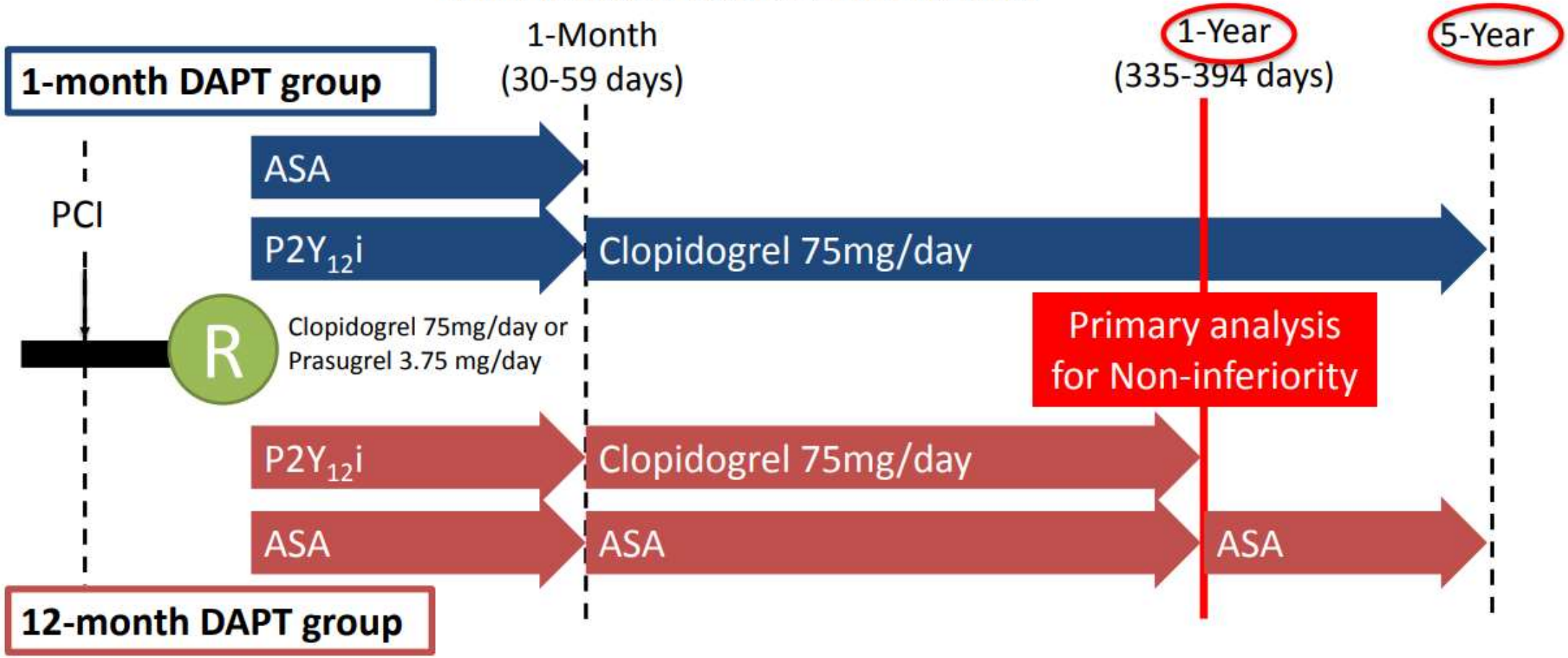
| Subgroup | Patients | MACCE (%) P2Y12 inhibitor monotherapy | MACCE (%) DAPT | Hazard ratio (95% CI) | P for interaction |
|---|---|---|---|---|---|
| Age | | | | | 0.90 |
| ≥65 years | 1534 | 33/791 (4.3) | 27/743 (3.8) | 1.16 (0.70–1.93) | |
| <65 years | 1459 | 9/704 (1.3) | 9/755 (1.2) | 1.09 (0.43–2.74) | |
| Sex | | | | | 0.92 |
| Male | 2198 | 28/1087 (2.6) | 24/1111 (2.2) | 1.20 (0.70-2.07) | |
| Female | 795 | 14/408 (3.6) | 12/387 (3.2) | 1.14 (0.53-2.47) | |
| ACS | | | | | 0.52 |
| Yes | 1741 | 25/870 (3.0) | 24/871 (2.9) | 1.06 (0.61-1.85) | |
| No | 1250 | 17/625 (2.8) | 12/625 (2.0) | 1.43 (0.68-3.00) | |
| Diabetes | | | | | 0.84 |
| Yes | 1122 | 23/570 (4.1) | 20/552 (3.8) | 1.13 (0.62–2.05) | |
| No | 1868 | 19/922 (2.1) | 16/946 (1.7) | 1.24 (0.64–2.40) | |
| P2Y12 inhibitor | | | | | 0.10 |
| Clopidogrel | 2312 | 34/1149 (3.0) | 34/1163 (3.0) | 1.02 (0.64-1.65) | |
| Prasugrel / Ticagrelor | 681 | 8/346 (2.4) | 2/335 (0.7) | 3.96 (0.84-18.66) | |
| Type of DES | | | | | 0.71 |
| CoCr-EES | 1051 | 12/525 (2.4) | 8/526 (1.6) | 1.54 (0.63-3.78) | |
| BP-SES | 972 | 13/481 (2.8) | 14/491 (2.9) | 0.95 (0.45-2.02) | |
| PtCr-EES | 967 | 17/489 (3.5) | 14/478 (3.0) | 1.20 (0.59-2.44) | |




Hahn JY, Song YB,…, Gwon HC. JAMA 2019.

# STOPDAPT-2:

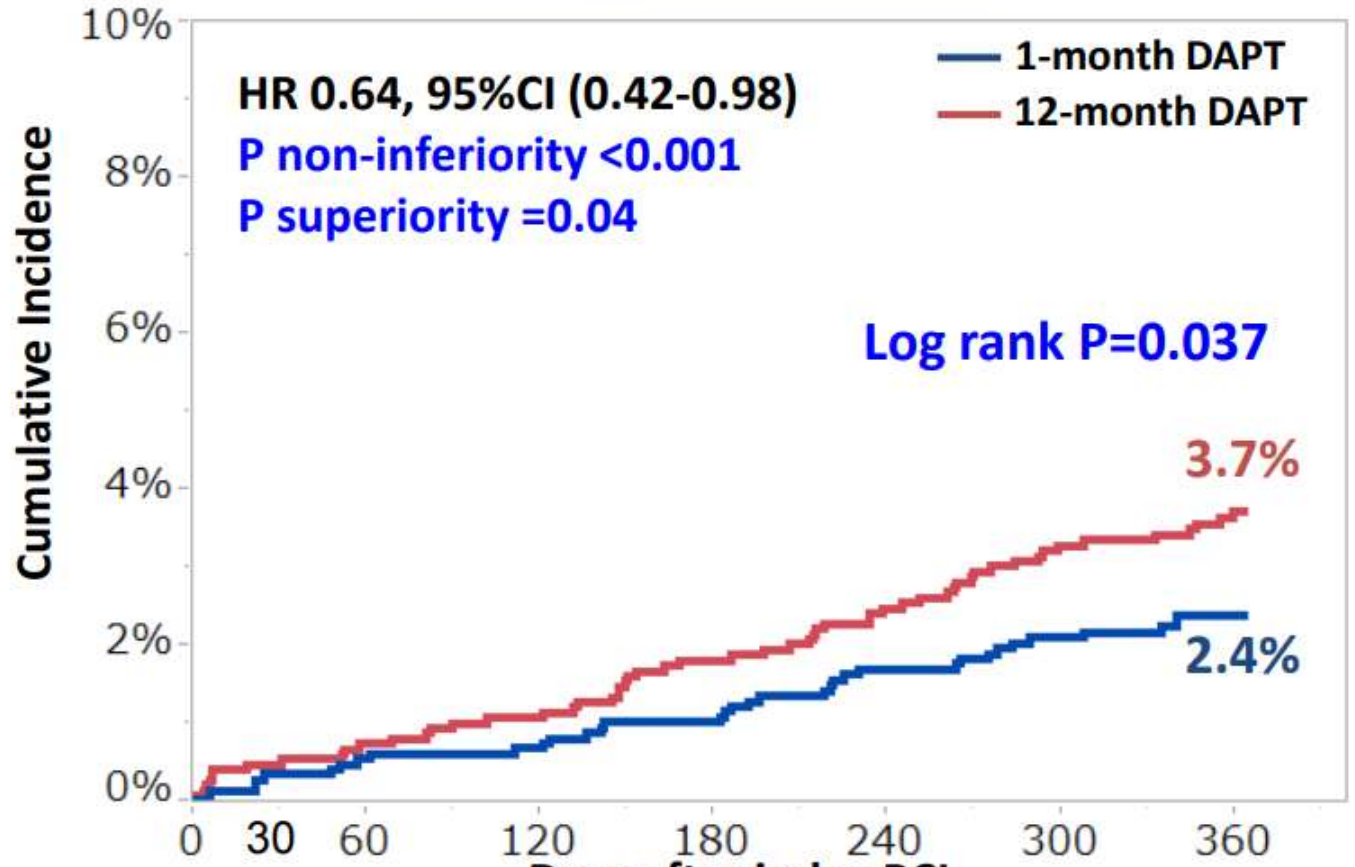
**Prospective multicenter open-label randomized trial comparing 1-month versus 12-month DAPT after CoCr-EES implantation with limited exclusion criteria.**




Watanabe et al. JAMA 2019

# Primary Endpoint: Net clinical benefit

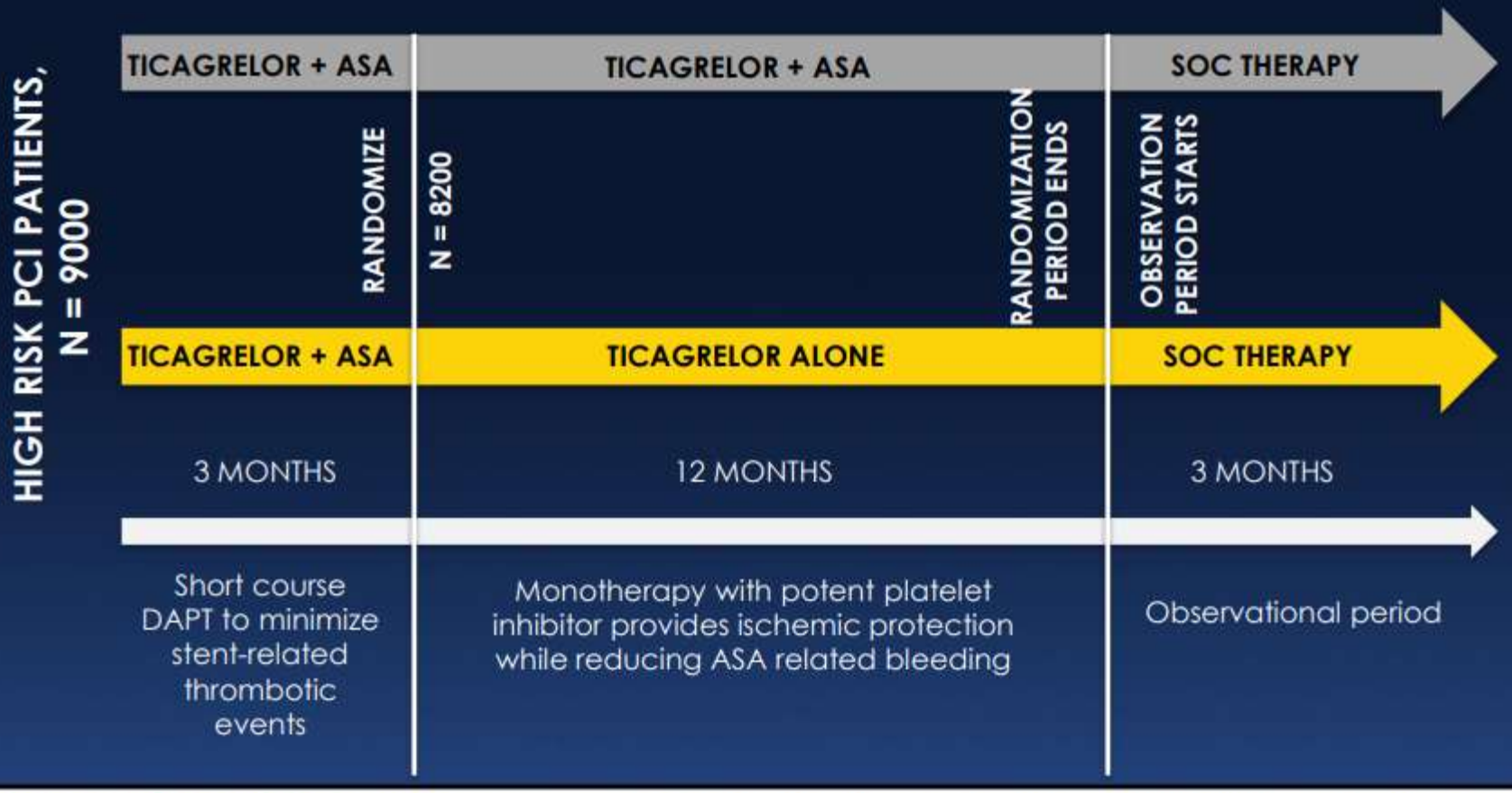
## CV death/MI/ST/Stroke/TIMI major/minor bleeding




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 12-month DAPT | 1509 | 1501 | 1486 | 1481 | 1469 | 1458 | 1442 | 1159 |
| 1-month DAPT | 1500 | 1494 | 1479 | 1475 | 1468 | 1453 | 1441 | 1151 |

Watanabe et al. JAMA 2019

# The TWILIGHT Study

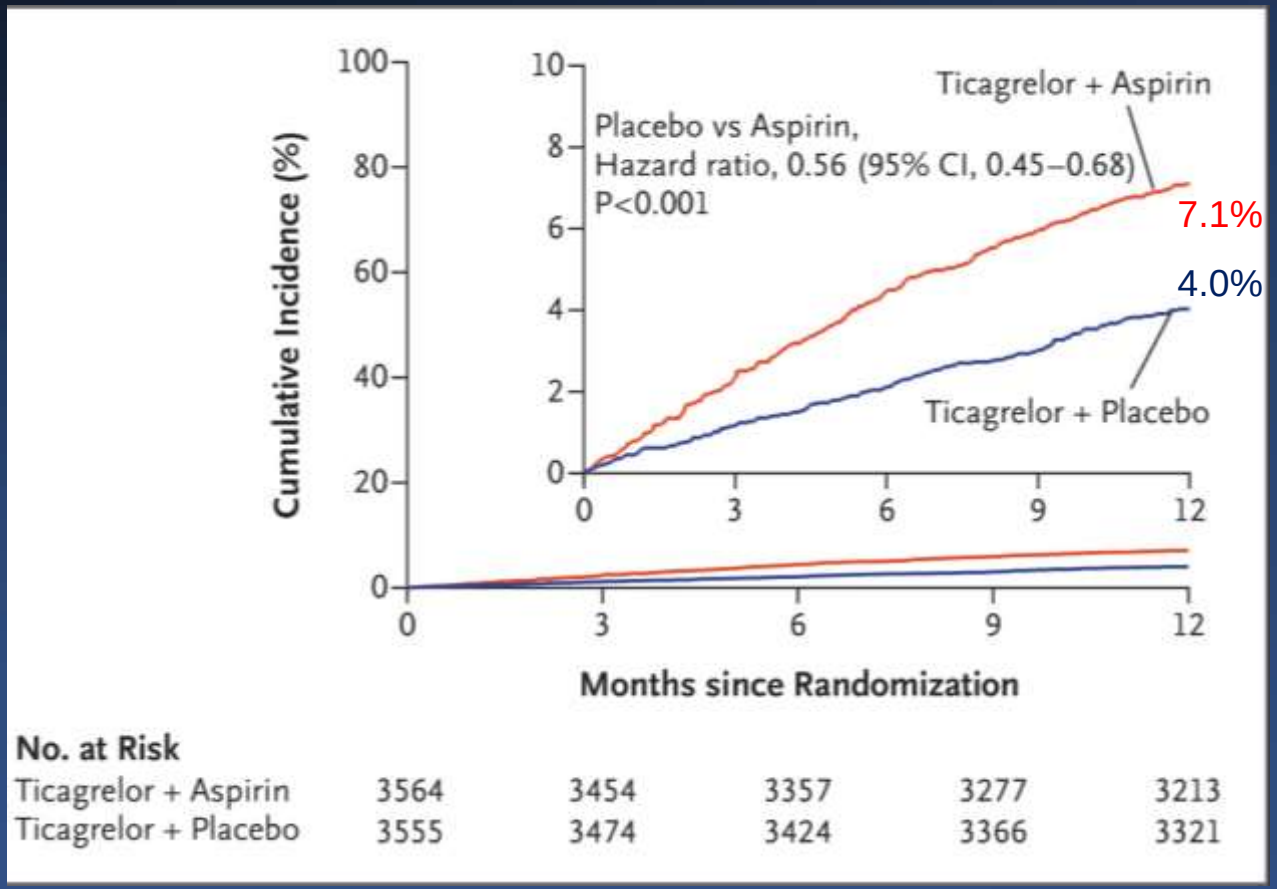



***Primary Hypothesis:*** ***3-month course of DAPT with ticagrelor plus aspirin followed by ticagrelor alone will be SUPERIOR to ticagrelor plus aspirin for 12 months with respect to clinically relevant bleeding (BARC ≥ 2) at 1 year***

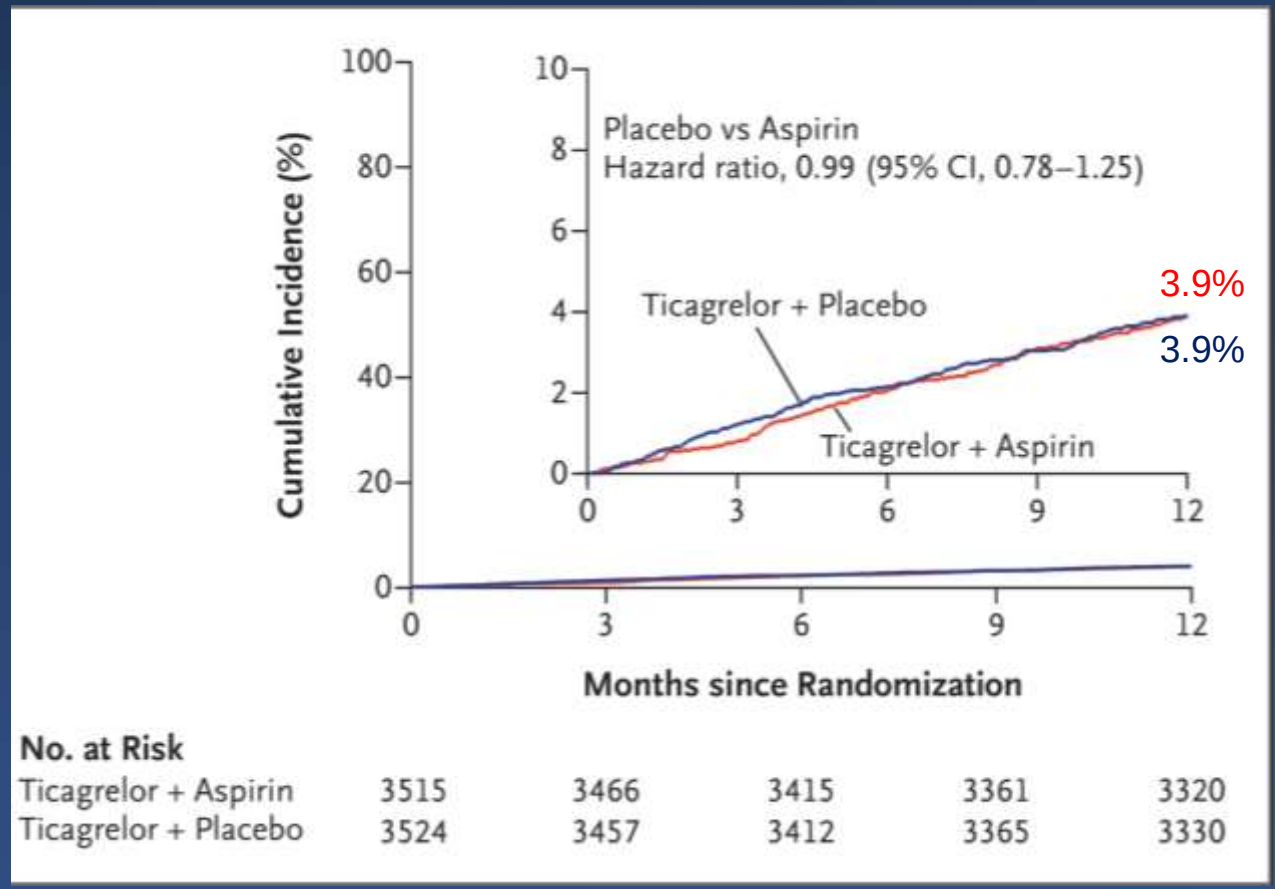
***Secondary Hypothesis:*** ***3-month course of DAPT with ticagrelor plus aspirin followed by ticagrelor alone will be will be NON-INFERIOR to ticagrelor plus aspirin for 12 months with respect to ischemic adverse events at 1 year***

# TWILIGHT: Study outcomes

## BARC Type 2, 3, or 5 Bleeding



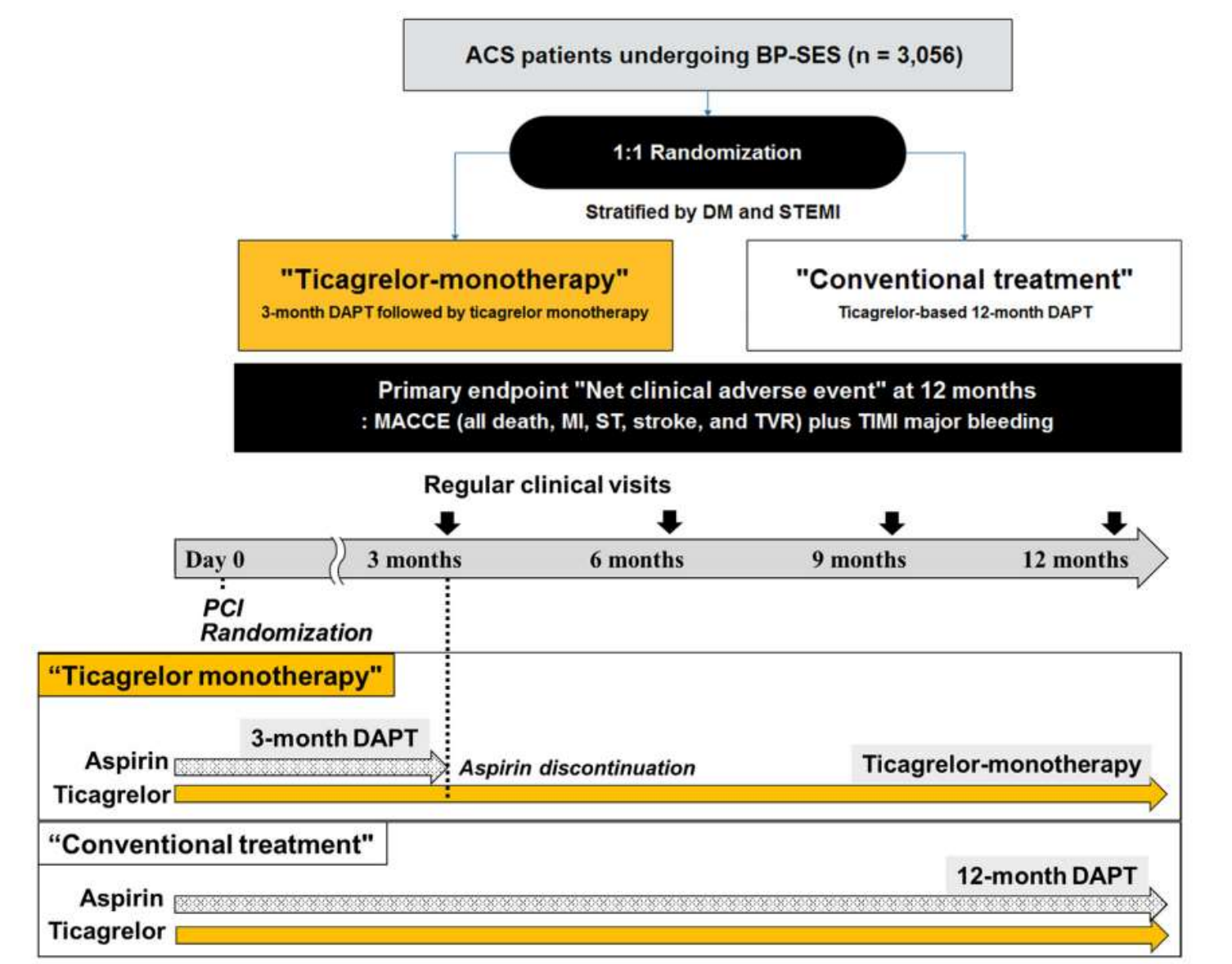

## Death, Nonfatal MI, or Nonfatal Stroke






Mehran R et al. N Engl J Med 2019

# TICO trial: Study design




Kim C, Kim BK, Hong MK et al. AHJ 2019

# Strategies to reduce the risk of bleeding after PCI

**Not for all**
**: ACS, complex PCI**


SMART-DATE

**Limited data**


TOPIC
TROPICAL-ACS
TALOS

**Promising novel strategy**


GLOBAL LEADERS
SMART-CHOICE
STOPDAPT-2
TWILIGHT
TICO